The web around patients with neuroendocrine tumors

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CHAPTER 8

Summary and future perspectives

Summary

Neuroendocrine tumors (NETs) constitute a rare and heterogeneous group of tumors. Most NETs arise in the gastroenteropancreatic tract or bronchopulmonary system, where they are derived from enterochromaffin cells. NETs can produce various biogenic amines and polypeptide hormones which can lead to various symptoms [1,2]. For example, patients with a serotonin producing NET can suffer from the carcinoid syndrome characterized by flushing, diarrhea, asthma-like symptoms (e.g. wheezing) and valvular heart disease [3]. Cure of patients with NETs can only be achieved by complete resection of the tumor. In case of non-curable disease, therapy often includes systemic treatment like long-term somatostatin analogues for control of disease progression and symptoms [4]. Most often, low grade (grade 1 and 2, according to World Health Organisation 2017 classification) NETs have a relative indolent nature with a 5-year overall survival of 55% in patients with metastatic disease [5]. So, patients can experience various symptoms for a long time due to the localization of the tumor as well as the release of bioactive substances secreted by the tumor. Also, side effects of the treatment itself can bother the patients.

NET patients experience a lower health related quality of life than the general population [6-8]. In general, when patients with cancer are properly informed, they experience a better health related quality of life and less depression and anxiety [9,10]. In addition, providing information also results in an increased participation of patients in decision making, greater satisfaction with care, lower levels of distress and improved sense of control [10-13]. Given these findings better ways of informing and supporting NET patients as well as novel treatments are warranted.

The aim of this thesis was to determine novel ways of informing, supporting and treating patients with a NET.

Chapter 1 is the general introduction and outlines this thesis.

In **Chapter 2** an extensive literature overview is given of the effects of internet-based support programs on psychosocial and physical symptoms resulting from cancer diagnosis and treatment. We searched the literature for (non-)randomized controlled trials performed in adult cancer patients comparing quantitative psychosocial and/or physical outcomes of an internet-based support program with (a) comparison group(s). 'Cancer patients' were defined as individuals diagnosed with any solid cancer type, irrespective of disease stage, treatment phase, type of treatment and time since diagnosis. An internet-based support program was defined as any program that aimed to rehabilitate or support cancer patients regarding psychosocial and/or physical symptoms resulting from diagnosis and treatment. The internet-based support program should have been designed by (a) health care professional(s). Studies regarding social support groups were eligible if the groups were moderated by a health care professional.

Studies that described programs without access to the internet (e.g. CD-rom or DVD) or to a website (e.g. therapy via e-mail) were excluded. Quantitative psychosocial variables such as distress, anxiety, depression, quality of life and physical variables such as fatigue, insomnia, pain and sexual problems were the outcomes of interest. The CINAHL, MEDLINE (PubMed) and PsychINFO data bases were searched from inception till the last search on 31th January 2014 without limitations. Relevant references from retrieved articles and relevant systematic reviews were also reviewed to identify other eligible studies. Only articles in English were included. Each included study was assigned a level of evidence according to the Oxford Centre of Evidence Based Medicine (ranging from score 1 (highest level) to score 5 (lowest level)). Our literature search yielded 2032 studies of which 16 fulfilled the eligibility criteria. Three different internet-based support programs were identified: social support groups, online therapy for psychosocial/physical symptoms and online systems integrating information, support and coaching services. Positive effects of the programs on outcomes were reported in nine studies. Especially fatigue, social support and distress improved, regardless of the program type. All online systems showed positive effects, mainly for social support and quality of life. The highest level of evidence of the included studies was score 2, which was the case in 12 studies. These findings indicated that internet-based support programs are effective in improving psychosocial and physical symptoms in cancer patients regardless of the used program type.

No internet-based support program was available for patients with a NET and therefore we developed a web-based system. This system allows patients to self-screen for physical and psychosocial problems, to get tailored patient education on reported problems and if necessary, to refer themselves to care.

In **Chapter 3** we examined the feasibility of our self-developed web-based system in newly diagnosed grade 1 and 2 NET patients and evaluated the patient's opinion on this. Patients were randomized between standard care (N = 10) or intervention with additional access to the web-based system (N = 10) during 12 weeks. The participation and dropout rate were calculated and reasons for declining participation or dropout were noted. Patients completed questionnaires regarding received information, distress, quality of life and empowerment. Effect sizes for change scores on each endpoint were determined (Cohen's *d*). A positive effect size indicated a desired direction (i.e. improvement of outcome in favor of the intervention group). The intervention group also completed a semi-structured interview to assess patients' opinion on the web-based system. The participation rate was 77% (20 of 26 invited patients) and all participants completed the study (0% dropout rate). The use of the web-based system had a negative effect on patients' perception and satisfaction of received information (range Cohen's *d* -0.88 to 0.13). Positive effects were found for distress (Cohen's *d* 0.75), global quality of life (subscale European Organization for Research and Treatment of Cancer Quality of Life

Questionnaire of cancer patients (EORTC QLQ-C30, Cohen's *d* 0.46), resolving problems with social functioning and finding information (subscales EORTC QLQ GINET 21 (quality of life questionnaire for neuroendocrine carcinoid patients), Cohen's *d* 0.69 respectively 1.04), and feeling informed (subscale empowerment questionnaire, Cohen's *d* 0.51). The semi-structured interview with the intervention group indicated that the web-based system was of additional value to standard care. All interviewed participants would like to use the web-based system in the future. From the results of this study we concluded that use of this web-based system for NET patients was feasible and that patients also appreciate this web-based system. However, we found conflicting effects of the web-based system on informing and supporting NET patients. Therefore, we conducted a randomized controlled follow-up study.

In **Chapter 4** this randomized controlled follow-up study is described. In this study, the effects of the web-based system on perceived distress, patients' perception of and satisfaction with received information, quality of life and empowerment of NET patients were analyzed. The web-based system was adapted based on patients' recommendations and results of the pilot study described in Chapter 3. Eligible participants were adult patients with grade 1 or 2 NET and who were proficient in Dutch, reading and writing. Patients were stratified by 'time since diagnosis', which resulted in 28 patients with newly diagnosed NET within <6 months and 74 patients longer known with NET disease. Patients were in a 1:1 ratio randomized between standard care (N = 49) or intervention consisting of standard care with additional access to the web-based system (N = 53). Patients completed questionnaires regarding distress, received information, quality of life and empowerment during the 12-week study period. At the end of the study period, the patients with access to the web-based system also completed a questionnaire about their use of and opinion about the web-based system. No differences between the control and intervention group were found for distress, patients' perception of and satisfaction with received information and quality of life. Empowerment, measured by different domains, was better in the control group, except for the domain 'optimism and control over future' for which no difference was found. The intervention group found the web-based system useful, interesting and of added value, had a positive attitude towards the web-based system en would recommend it to peers. The median score of the questionnaire was 4 on a 5-point Likert scale ranging from 1 to 5. In conclusion, the web-based system did not improve distress, patients' perception and satisfaction of received information, and quality of life more than standard care in NET patients. Empowerment was better in the patients receiving standard care. However, the intervention group had a positive opinion about the use of the web-based system.

In **Chapter 5** we assessed the feasibility of video-consultation in the follow-up care of clinical stable patients with NET. Patients with NETs are increasingly treated in expert centers which leads to longer travel times for medical consultations. Given the

general course of their disease, frequent hospital visits are required for a long time. Video-consultation potentially allows remote guidance of patients and therefore saves time for patients. Calculation of participation and dropout rate, reasons for declining participation, reasons for dropout and safety concerns were used to asses feasibility. In this study, 20 patients received two video-consultations during one year of follow-up. Questionnaires were used to measure satisfaction with video-consultation by patients and physicians. Also, the duration of a video-consultation, the patient-reported travel time for a regular outpatient clinic visit and the patient's preference for type of consultation were recorded. Reasons for no study participation were 'patient's preference for consultation at the outpatient clinic', 'no internet experience by the patient' and 'medical condition does not allow video-consultation'. Twenty-six of the 31 invited patients participated in the study. Six participants did not complete the full study. Reasons for dropout were 'medical condition does not allow video-consultation', 'physicians' preference for outpatient clinic consultation', 'technical problems', 'death of patient' (N = 1, not related to video-consultation) and 'follow-up of patient in another hospital'. No safety concerns were reported. Median score for satisfaction of patients and physicians were 4.6 ranging from 3.3-4.9 on the five-point Likert scale and 4.0 ranging from 3.5-4.9 respectively, indicating high satisfaction with video-consultation. Technical problems leading to prolonged connection time and impaired audio/video quality were reported by 55% of the patients and 40% of the physicians. The median duration of a video-consultation was 13 minutes with a range of 9-25 minutes. The patient-reported duration of a follow-up consultation at the outpatient clinic was 240 minutes ranging from 100-390 minutes. Sixty percent of the patients preferred video-consultation. We demonstrated that use of video-consultation during follow-up care of patients with clinical stable NET is feasible. From these data we concluded that the patients' and physicians' acceptability and satisfaction with video-consultation is high, but can be further improved, particularly by solving technical problems.

Nowadays, there is still an ongoing need and search for new treatment modalities for patients with a NET. The essential amino acid tryptophan is the precursor for serotonin and nicotinamide adenine dinucleotide (NAD+), the metabolically active form of niacin (vitamin B3). In serotonin-producing NET patients, the tryptophan is consumed for serotonin production which can result in deficiency of tryptophan and niacin. A variety of symptoms and complaints related to the skin, gastrointestinal tract and nervous system can be seen with tryptophan and/or niacin deficiency. Best known is pellagra, which is characterized by 'the four Ds': dermatitis, diarrhea, dementia and death. In patients with serotonin-producing NETs, pellagra and other symptoms suggestive of tryptophan and/or niacin deficiency are reported. Niacin supplementation resulted in a quick and substantial improvement of symptoms in these patients. **Chapter 6** describes a study in which we examined the niacin status in 42 patients with a serotonin-producing NET

and with tryptophan deficiency and/or associated symptoms, who therefore received oral niacin supplementation. Niacin status was measured by 24-hour output of urinary N^1-methylnicotinamide (N^1-MN), which is a reliable marker for assessing niacin status. N^1-MN was serially assessed before and after supplementation to examine the effectiveness of niacin supplementation. Reference values for urinary N^1-MN levels were established in 133 healthy individuals. In the 42 patients with NETs the mean plasma tryptophan level was 31.8 ± 9.7 µmol/L (reference value 40.0-70.0 µmol/L) before supplementation. Presupplementation urinary N^1-MN levels were lower in patients (median 17.9 µmol/24-hour, range 2.6-70.3) compared to healthy controls (median 43.7 µmol/24-hour, range 9.5 – 169.3, $p<0.0001$) and below normal in 45% of the patients. With niacin supplementation urinary N^1-MN levels increased to high normal levels (median 55.5 µmol/24-hour, range 7.4 – 489.0). Eventually, 86% of the niacin-deficient patients had a normal niacin status after supplementation. In conclusion, niacin supplementation was effective in normalizing niacin status in previously niacin-deficient patients.

In **Chapter 7** we investigated the tumor microenvironment of NETs to search for potential treatment targets. Tumor tissues of 51 patients with a grade 1 or 2 NET, collected before start of systemic antitumor treatment, were selected. Immunohistochemical analyses of the tumor tissues were performed for programmed death ligand 1 (PD-L1), T-cells (recognized by CD3-staining), indoleamine 2,3-dioxygenase (IDO), tryptophan 2,3-dioxygenase (TDO), mismatch repair proteins and activated myofibroblast and/or myofibroblast-like cells (recognized by alpha-smooth muscle actin and desmin-staining). Before start of systemic antitumor treatment, serotonin was measured by high performance liquid fluorometry of 5-hydroxyindolacetic acid (5-HIAA) in 24-h urine and/or serotonin in platelet rich plasma of the included patients. Tumors of 33 patients with a serotonin-producing NET and 18 patients with a non-serotonin-producing NET were studied. None of the tumor cells and T-cells expressed PD-L1. T-cells were present in 15 out of 45 evaluable NETs, varying between 1-10% T-cells per high power field. T-cells were not infiltrating between tumor cells, but most frequently found within the stroma of NETs of the jejunum/ileum which were all serotonin-producing NETs. IDO was more often expressed in serotonin-producing NETs namely in 18 out of 33 (55%) and 4 out of 18 (22%) of non-serotonin-producing NETs ($p = 0.039$). Unexpectedly, TDO showed prominent staining in stroma in 18 out of 41 (44%) evaluable NETs. TDO was expressed in stromal cells in 16 out of 25 evaluable serotonin-producing NETs and two out of 16 evaluable non-serotonin-producing NETs ($p = 0.001$). Seventeen out of 46 (37%) evaluable NETs had TDO staining in tumor cells. None of the tumors had loss of mismatch repair proteins. Tumors with TDO expressing stromal cells also strongly expressed alpha-smooth muscle actin and desmin, and were therefore identified as cancer associated fibroblasts.

We concluded that NETs have a cold immune microenvironment as they do not express PD-L1, contain only few tumor infiltrating T-cells and have no loss of mismatch repair proteins. We suggest that the cold immune microenvironment of neuroendocrine tumors is at least partly the result of IDO and/or TDO expression and the presence of cancer associated fibroblasts.

Future perspective

In this thesis we have addressed several aspects of informing, supporting and treating patients with a NET. Due to the rarity of NETs, it is difficult for patients to gather information about their disease and to get support. In the Netherlands, NET patients have the possibility to receive information and support via the Dutch Patient Neuroendocrine Tumour Foundation [14]. Also, treating a patient with a NET can be a challenge for health care professionals. Therefore, in the Netherlands most NET patients are treated in the so-called 'ENETS (European NeuroEndocrine Tumor Society) centers of excellence' [15]. This often coincides with relatively long travel distances for patients. It is known, that patients with NETs experience the burden of travelling to a NET center/expert, although travel distances in the Netherlands are limited [8]. Informing and supporting these patients via a web-based system is a novel tool which gives the patient an additional option for gathering information and support 24-hours a day. Internet-based support programs are effective in improving psychosocial and physical symptoms in cancer patients, as we concluded in our review in Chapter 2. In patients with NETs, however, we found conflicting results of our self-developed web-based system on informing and supporting in the pilot study (Chapter 3) and no improvement in distress, perceived information and quality of life in the randomized controlled follow-up study (Chapter 4). Although no positive effects could be found, most patients have the opinion that this web-based system should be part of standard of care and pointed out they would like to use it in the future. In this 'internet era', it is inevitable that these patients demand the ability of receiving online information and support. However, a web-based system will never replace the information and support given face-to-face by their well-known treating health care professional. Further research has to address how the web-based system can be adapted and has to be used to improve perceived information and support. For example, adding more visual illustrations can enhance insight and improve recall of information. This finding has been observed in older colorectal cancer patients who used a website to retrieve cancer information [16]. Also, it is unknown which factors (e.g. psychosocial, clinical, disease-related, internet) are associated with the use and effects of the web-based system in patients with NET. In our study, the web-based system has been used for a short time namely 12 weeks with a short follow-up period. Consequently, effects of long term use during the course of the disease and long term effects of the

web-based system are unknown. In a future study with a larger sample size, it is desirable to investigate which factors are associated with the use and positive effects of the web-based system. Also, the effects of longer use of the web-based system and long term effects deserve further attention. To get a better insight in the effect of the web-based system on patients' empowerment a new validated empowerment questionnaire has to be developed, which can be used for a pre- and post-assessment in future studies.

As described in Chapter 5 video-consultation can be used for easier access to a NET expert and to reduce the burden of travelling for patients with NETs. Video-consultation is a good alternative for an outpatient clinic consultation in clinical stable NET patients having experience with internet/video communication and not requiring physical examination. Since January 2018, a follow-up consultation performed with a video-consultation is in the Netherlands reimbursed as a face-to-face consultation at the outpatient clinic by health care insurances. This can be an extrinsic motivation to conduct (more) video-consultations. However, drawbacks in conducting video-consultations are technical problems as well as concerns about safety (e.g. safe internet connection) and privacy regulations. For good and adequate implementation of video-consultation in standard care, technical problems have to be addressed and a 'patient- and health care professional-friendly' video-consultation application meeting all safety and privacy regulations is required. In our study, we noted that communication with caregivers and/or family of a patient with a NET is less intense and hampered by video-consultation compared to a consultation at the outpatient clinic. For example, caregivers/family joining the patient were sometimes (partly) outside the view of the camera. Also, it can be more difficult for accompanying caregivers/family to participate in the conversation during a video-consultation. Further research is warranted to investigate if caregivers and family members experience a lack of communication or interaction during video-consultation and if this has a negative effect on patients' health (care) and quality of life. Some of the used questionnaires for patients in the study described in Chapter 5 can be adapted to use it for caregivers and family member. Results of these questionnaires can be correlated with patients' reported quality of life.

Treating patients with NETs in referral centers, has raised awareness and recognition of their specific complaints and problems. For example, signs and symptoms of tryptophan and/or niacin depletion due to serotonin-producing NETs are better recognized. As a result, patients with tryptophan and/or niacin deficiency receive earlier treatment with nicotinamide and thereby pellagra or other symptoms can be prevented. As shown in Chapter 6, oral supplementation of nicotinamide in niacin deficiency is easy and effective. Niacin is a water-soluble vitamin and thereby not stored in the body, which requires daily oral administration of niacin supplementation [17]. Further prospectively designed research is required to determine the correct dose of nicotinamide supplementation by assessment of urinary N^1-MN. Here is of interest

to include urinary N^1-MN in the biochemical assessment of serotonin production at diagnosis and during follow-up to establish niacin deficiency on time before symptoms occur. In addition, patients can be informed about the usefulness and correct intake of niacin supplementation and symptoms associated with niacin deficiency.

To search for new treatment modalities in patients with grade 1 and 2 NETs, such as immunotherapy, we established the tumor immune microenvironment as described in Chapter 7. We found a 'cold' tumor immune microenvironment in NETS with absence of PD-L1 expression, limited presence of T-cells, substantial expression of IDO and/or TDO and presence of CAFs. It is expected that use of solely an immune checkpoint inhibitor in patients with NETs is ineffective due to this cold tumor immune microenvironment. Only few data is available on the use of immune checkpoint inhibitors in grade 1 and 2 NETs. The KEYNOTE-028 study was a multicohort phase 1b study including heavenly pre-treated grade 1 and 2 PD-L1-positive NETs of the pancreas (N = 16) and carcinoids (N = 25, primary site in the lung, gut or other organ) which were treated with the PD-1 inhibitor pembrolizumab [18]. Four patients experienced a partial response and 13 patients had stable disease for more than 6 months. In the multicohort phase 2 KEYNOTE-158 study, 107 patients with well- and moderately differentiated NETs of several primary sites progressive on or intolerant to more than one line of standard treatment were treated with pembrolizumab [19]. The overall response rate was 3.7%, which was observed as a partial response in 4 patients with a PD-L1 negative tumor. Patients with high grade neuroendocrine tumors demonstrate better responses on immunotherapy. In a phase II trial, 29 patients with metastatic progressive neuroendocrine carcinoma, grade 3 according to WHO 2010, of several sites of origin were treated with the PD-L1 antibody avelumab. After 8 weeks of treatment 32% of the patients had stable disease or partial remission [20]. Dual checkpoint blockade with the PD-1 inhibitor nivolumab and the anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) agent ipilimumab given to 33 patients with low-, intermediate- and high-grade NETs in a phase II trial resulted in an overall response rate of 24%, one complete response and seven partial responses, which were all patients with high-grade NETs [21]. An explanation for the better response in high grade NETs may be the presence of a higher tumor mutational burden.

To enhance the efficacy of immune checkpoint inhibitors in NETs, a transformation into a 'hot' tumor immune microenvironment of NETs might be of interest. Potential opportunities, although still uncertain, are combining immune checkpoint inhibitors with therapies which achieve increase of PD-L1 expression and/or tumor infiltrating T-cells or inhibition of IDO and/or TDO expression. Combination therapy of an IDO and/or TDO-inhibitor with immune checkpoint inhibitors (e.g. PD-1 or PD-L1 inhibitor) is theoretically an interesting strategy for NETs, which has not yet been studied. However, in patients with unresectable or metastasized melanoma, the combination of the IDO-inhibitor epacadostat with the PD-1 inhibitor pembrolizumab versus pembrolizumab

in a phase III-study lacked effect on progression-free or overall survival [22]. Given these and other disappointing results of studies conducted in patients with several tumor types treated with a combination of IDO and PD-1 inhibitor the enthusiasm is currently tempered for this approach.

At this moment, the safety and tolerability of an IDO1/TDO dual inhibitor is evaluated in 30 patients with advanced solid tumors in a phase I study (ClinicalTrials.gov Identifier: NCT03208959). This novel IDO/TDO dual inhibitor might be of interest in the treatment of NET patients given the substantial expression of IDO and/or TDO in neuroendocrine tumors.

Interferon is a standard treatment in patients with a metastasized NET which can relieve the symptoms of a carcinoid syndrome and can have antitumor efficacy [23,24]. In a mice study, interferon led to induction and maintenance of PD-1 on T-cells and PD-1 expression on antigen-specific CD8 positive T-cells was augmented [25]. Combination treatment of interferon with PD-1 inhibitors might deserve a trial in patients with NETs given the results of aforementioned studies.

Another unexplored field in NETs is the role of circulating regulatory T-cells which are associated with suppression of tumor infiltrating T-cells and natural killer (NK) cells. In a currently recruiting study, patients with metastasized or unresectable NETs with a low proliferation rate (tumor proliferation marker Ki67 ≤10%) are treated with cyclophosphamide and interferon-alpha to evaluate if this treatment regimen decreases the rate of circulatory regulatory T-cells (ClinicalTrials.gov Identifier: NCT02838342).

In conclusion, it is worth to consider and examine new strategies to overcome tumor-induced immune tolerance in NETs as this might allow immune therapy in the future.

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